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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,722	WALLACH ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *104-119* is/are pending in the application.

4a) Of the above claim(s) *112-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (which now corresponds to claims 104-111) and the species election of SEQ ID NO: 22 in the reply filed on 6 November 2006 is acknowledged. The Supplemental Response, filed 4 December 2006 is also acknowledged.

The traversal is on the grounds that the amended claims do not read on the Sugamura et al., reference because the claims have been amended to recite only the intracellular domain of the IL-2R cγc chain. This is not found persuasive because the originally presented claims lack the same or corresponding special technical feature. The originally filed claims lacked unity of invention over Sugamura et al., US Patent 5,510,259 (23 April 1996), as stated in the Requirement for Restriction Election mailed 7 August 2006. Applicant has since cancelled all of the originally presented claims and has added new claims 104-119. New claims 104-111 correspond to originally filed Group II. New claims 112-114 correspond to originally filed Group III. New claim 115 corresponds to original Group IV, and new claims 116-119 correspond to original Group V. Because the originally presented claims lacked a special technical feature, and thus, lacked unity, the requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-103 have been cancelled by Applicants. New claims 104-119 have been added. Applicant elected Group II, drawn to a polypeptide fragment and elected a species of SEQ ID NO: 22. Amended claims 104-107 are drawn to the elected group and elected species. Claims 108-119 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 104-107 and the species of SEQ ID NO: 22 are under examination.

Specification

3. The use of the trademark CLONTECH (p. 47) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 104-107 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims recite a polypeptide capable of binding to NIK comprising (a) the intracellular domain of cγc (residues 284-269 SEQ ID NO: 22), or (b) a fragment of (a) that retains the ability to bind NIK, or (c) a variant of (a) or (b) maintaining at least 90% identity with (a) or (b) and retaining the ability to bind NIK, or (d) a salt or functional derivative of (a), (b), or (c) that retains the ability to bind NIK, or (e) a circularly permutated derivative of (a), (b), or (c) that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cγc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising 41MDD (residues 329-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising ICDcγc (residues 284-369 of SEQ ID NO:22); a polypeptide in accordance with claim 104, comprising the polypeptide of residues 289-369 of SEQ ID NO: 22.

The claims read on the naturally occurring intracellular domain of a cγc polypeptide that binds to NIK. As such, the claims are directed to non-statutory subject matter. Applicant may overcome this rejection by narrowing the claims to encompass only isolated or purified polypeptides with the desired activity that do not read on naturally occurring subject matter.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 104-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide consisting of residues 329-369 of SEQ ID NO: 22 that binds to NIK, does not reasonably provide enablement for the claimed genus of polypeptides capable of binding to NIK comprising: (a) the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22), or (b) a fragment of (a) that retains the ability to bind NIK, or (c) a variant of (a) or (b) maintaining at least 90% identity with (a) or (b) and retaining the ability to bind NIK, or (d) a salt or functional derivative of (a), (b), or (c) that retains the ability to bind NIK, or (e) a circularly permutated derivative of (a), (b), or (c) that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cγc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a polypeptide capable of binding to NIK comprising (a) the intracellular domain of cγc (residues 284-269 SEQ ID NO: 22), or (b) a fragment of (a) that retains the ability to bind NIK, or (c) a variant of (a) or (b) maintaining at least 90% identity with (a) or (b) and retaining the ability to bind NIK, or (d) a salt or functional derivative of (a), (b), or (c) that retains the ability to bind NIK, or (e) a circularly permutated derivative of (a), (b), or (c) that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cγc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising 41MDD (residues 329-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising ICDcγc (residues 284-369 of SEQ ID NO:22); a polypeptide in accordance with claim 104, comprising the polypeptide of residues 289-369 of SEQ ID NO: 22.

The nature of the invention is drawn to a polypeptide that binds to NIK, a kinase involved in NFκβ activation. The state of the art discloses that NIK is a member of the MAP kinase family (see Rothe et al., US Patent 5,844,073, 1 December 1998, column 1, lines 64-65). NIK is also a critical component in the activation of the NFκβ pathway. It was identified as a TRAF2-interacting protein that contained a serine/threonine protein kinase motif resembling MAP3K proteins (Malinin et al., Nature.

1997 Feb 6;385(6616):540-4, Abstract Only). Overexpression of NIK leads to activation of NFκβ, but not JNK (Song et al., PNAS USA 1997 Sep 2;94(18):9792-6, Abstract Only), and NIK is required for activation of the alternative pathway characterized by p100 processing (Dejardin et al., Immunity. 2002 Oct;17(4):525-35, Abstract Only). More recent studies demonstrate that depletion of NIK by siRNA blocked the activation of both the classical and alternative NFκβ pathways by CD27, CD40 and BAFF-R, but not by TNFRI, which is restricted to activating RelA/p50 complex through the classical pathway (Ramakrishnan et al., Immunity. 2004 Oct;21(4):477-89, Abstract Only). These findings suggest a role for NIK in facilitating the activation of both NFκβ pathways by receptors that harbor NFκβ capability, but not in triggering the classical pathway by single NFκβ -inducers like TNFRI. Multiple functions for the IL-2 common gamma chain receptor are elucidated by O'Connell et al., J Mol Evol., 2005; 61:608-619. The level of skill of those in the art is high due to the multifactoral parameters associated with intracellular signaling pathways and proteins that bind to each other in various signaling cascades.

There are four working models of polypeptides that bind to NIK. They are 41MDD (residues 329-369 of SEQ ID NO: 22), 44MPD (residues 282-325 of SEQ ID NO: 22), 1-357 and 1-341 (see specification pp. 48, Table 1; p. 49, Table 2; p. 51, Table 3; and p. 58, Table 4). However, none of the examples teach a polypeptide capable of binding to NIK comprising the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22). None of the examples teach salts or functional derivatives of a polypeptide capable of binding to NIK comprising the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22. None of the examples teach variants with at least 90% identity to the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22) or variants of fragments of residues 284-369 of SEQ ID NO: 22 that retain the ability to bind to NIK. None of the examples teach salts or functional derivatives of variants, fragments, or variants of fragments with at least 90% identity to the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22) that retain the ability to bind to NIK. None of the examples teach a circularly permutated derivative that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cγc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22).

Claims 104-107 are directed to a genus of polypeptides, variants, fragments, and circular permutated derivates. The specification discloses four specific polypeptides that bind to NIK. Based on the potential structural similarity of the fragments, variants, and circular derivatives, the specification asserts that the claimed genus of generic variants, fragments, and circular permutated derivates have similar activities.

The assertion that the disclosed genus of generic variants, fragments, and circular permutated derivates have biological activities similar to recited four polypeptides cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997,

Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

General guidance is given regarding how to make and test variants of any protein. The scope of the patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Due to

the large quantity of experimentation necessary to generate the substantial number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant's claims are excessively broad. For example, claim 104 recites a polypeptide capable of binding to NIK comprising a fragment of residues 284-369 of SEQ ID NO: 22 that retains the ability to bind NIK. However, neither the art nor the specification provide any guidance on which portion of the 85 or so residues from the intracellular domain portion of SEQ ID NO: 2 are required in order to bind to NIK. It is unclear how long or short the claimed fragment is intended to be. There is no guidance to suggest that the claimed binding requires more than the binding of one amino acid to NIK. Without knowing which residues are critical for binding to NIK the recited binding would be unpredictable. The genus of fragments claimed is not supported in the specification such that one of ordinary skill in the art would be able to make and use the genus without undue experimentation.

Applicant's claims are also excessively broad because they read on any salt or functional derivative of any peptide that has the ability to bind to NIK. For example, claim 104, part (d) recites a polypeptide capable of binding to NIK comprising a salt or a functional derivative of (a), (b), or (c) that retains the ability to bind to NIK. There is no guidance in the specification that teaches how to make or use the genus of claimed polypeptides, salts, or functional derivatives that retain an ability to bind to NIK. The definitions of "salts" and "functional derivatives" on page 23 of the specification provides no assistance in this regard. It would require undue experimentation to determine a sufficient number of species of polypeptides, salts, and functional derivatives. Without sufficient guidance, determining which polypeptides, salts, and functional derivates would bind to NIK would be entirely unpredictable.

Applicant's claims are also excessively broad in the recitation of a circularly permutated derivative of (a), (b), or (c), as recited in claim 104, part (e). There is no teaching of circularly permuted molecules outside of their definition on pages 23-24 of the specification.

Applicant's claims directed to variants of residues 284-369 of SEQ ID NO: 22 that are at least 90% identical thereto or fragment variants of residues 284-369 of SEQ ID NO: 22 that are at least 90% identical and retain an ability to bind NIK are not taught in the specification. The specification fails to teach or provide any guidance on what would constitute a polypeptide with 90% homology to variants of

fragments of residues 284-369 of SEQ ID NO: 22, let alone salts, or functional derivatives thereof (as recited in claim 104, parts (c) and (d). None of the examples teach variants with at least 90% identity to the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22) or variants of fragments of residues 284-369 of SEQ ID NO: 22 that retain the ability to bind to NIK. As such, the determination of which polypeptide variants, fragments, salts, or functional derivatives with at least 90% homology to residues 284-369 of SEQ ID NO: 22, retain the ability or are capable of binding to NIK, is entirely unpredictable and would require undue experimentation.

Claims 106 and 107 recite polypeptides of claim 104 comprising residues 284-369 (claim 106) and residues 289-369 (claim 107) of SEQ ID NO: 22. However, the specification fails to teach polypeptides comprising the residues of 284-369 or 289-369 with the required function of being capable of binding to NIK. Instead, the specification recites only he following polypeptides 41MDD (residues 329-369 of SEQ ID NO: 22), 44MPD (residues 282-325 of SEQ ID NO: 22), 1-357 and 1-341 (see specification pp. 48, Table 1; p. 49, Table 2; p. 51, Table 3; and p. 58, Table 4) as being capable of binding to NIK, along with TRAF2, which is not claimed. It would require undue experimentation to determine how to make or use a polypeptide variant, fragment, salt, functional derivative, or circularly permutated derivative of residues 284-369 or residues 289-369 that is capable of binding to NIK.

The claims fail to recite specific structural and functional limitations for the claimed genus of polypeptides, fragments, variants, variants of fragments, including those that are 90% homologous, salts, or functional derivates of any of the foregoing, or circular permutated derivatives of the intracellular domain of cγc (residues 284-369 of SEQ ID NO: 22) that are capable of binding to NIK. Additionally, the functional requirement for being "capable of binding to NIK" (as claimed) is not limited to polypeptides that actually bind NIK. As such, one of ordinary skill in the art would not know how to make or use the claimed invention.

There is no teaching or guidance in the specification to support the negative limitation in claim 104, part (e), which specifically limits the polypeptide to no more of the cγc sequence than the intracellular domain thereof. There are examples, such as 41MDD and 44MPD, which are comprised of sequences from the intracellular domain, but there is no disclosure anywhere in the specification that specifically limits the polypeptide to only the intracellular region of SEQ ID NO: 22 (residues 284-369).

Therefore, based on the discussions above concerning the art's recognition that neither the NIK pathway nor the proteins that bind to NIK are fully understood, the specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to determine how to

make or use a polypeptide, variant, fragment, salt, functional derivative, or circularly permutated derivative of residues 284-369 or residues 289-369 that is capable of binding to NIK.

Due to the large quantity of experimentation necessary to determine which polypeptides, variants, fragments, salts functional derivatives, or circularly permutated derivatives of residues 284-369 or residues 289-369 are capable of binding to NIK, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that the NIK pathway has not been fully elucidated, and the breadth of the claims which fail to recite specific structural and functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 22-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a polypeptide capable of binding to NIK comprising (a) the intracellular domain of cγc (residues 284-269 SEQ ID NO: 22), or (b) a fragment of (a) that retains the ability to bind NIK, or (c) a variant of (a) or (b) maintaining at least 90% identity with (a) or (b) and retaining the ability to bind NIK, or (d) a salt or functional derivative of (a), (b), or (c) that retains the ability to bind NIK, or (e) a circularly permutated derivative of (a), (b), or (c) that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cγc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising 41MDD (residues 329-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising

ICDcyc (residues 284-369 of SEQ ID NO:22); a polypeptide in accordance with claim 104, comprising the polypeptide of residues 289-369 of SEQ ID NO: 22.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., polypeptides, variants, fragments, salts, functional derivatives, with or without at least 90% homology to residues 284-369 of SEQ ID NO: 22, or circularly permutated derivates thereof that are capable of binding to NIK.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There are four species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* 41MDD (residues 329-369 of SEQ ID NO: 22), 44MPD (residues 282-325 of SEQ ID NO: 22), 1-357, and 1-341 (see specification pp. 48, Table 1; p. 49, Table 2; p. 51, Table 3; and p. 58, Table 4). The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

The specification fails to provide an adequate description of specific structural and functional limitations for the claimed genus of polypeptides, fragments, variants, variants of fragments, including those that are 90% homologous, salts, or functional derivates of any of the foregoing, or circular permutated derivatives of the intracellular domain of cyc (residues 284-369 of SEQ ID NO: 22) that are capable of binding to NIK, such that one of ordinary skill in the art would be aware that Applicant was in possession of the claimed genus of polypeptides, variants, fragments, homologues, or circularly permutated derivatives.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is polypeptides, variants, fragments, salts, functional derivatives, with or without at least 90% homology to residues 284-369 of SEQ ID NO: 22, or circularly permutated derivates thereof that are capable of binding to NIK. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, First Paragraph

Written Description - New Matter

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 104-107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite a polypeptide capable of binding to NIK comprising (a) the intracellular domain of cyc (residues 284-269 SEQ ID NO: 22), or (b) a fragment of (a) that retains the ability to bind NIK, or (c) a variant of (a) or (b) maintaining at least 90% identity with (a) or (b) and retaining the ability to bind NIK, or (d) a salt or functional derivative of (a), (b), or (c) that retains the ability to bind NIK, or (e) a

circularly permutated derivative of (a), (b), or (c) that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cγc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising 41MDD (residues 329-369 of SEQ ID NO: 22); a polypeptide in accordance with claim 104 comprising ICDcγc (residues 284-369 of SEQ ID NO:22); a polypeptide in accordance with claim 104, comprising the polypeptide of residues 289-369 of SEQ ID NO: 22.

There is no description or disclosure in the specification to support the negative limitation in claim 104, part (e), which specifically limits the polypeptide to no more of the cγc sequence than the intracellular domain thereof. There are examples, such as 41MDD and 44MPD, which are comprised of sequences from the intracellular domain, but there is no disclosure anywhere in the specification that specifically limits the polypeptide to only the intracellular region of SEQ ID NO: 22 (residues 284-369). As such, claims 104-107 are new matter.

Claim Rejections - 35 USC § 112, Second Paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 104-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite the functional requirement for being "capable of binding to NIK." However, being capable of binding to NIK is not limited to polypeptides that actually bind NIK. Thus, the metes and bounds of the functional limitations for the recited genus of polypeptides are undefined. No information is provided in the specification as to what it means to be "capable of binding."

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 104 is rejected under 35 U.S.C. 102(b) as being anticipated by Rothe et al., US Patent 5,844,073 (1 December 1998).

The claims recite a polypeptide capable of binding to NIK comprising (a) the intracellular domain of cyc (residues 284-269 SEQ ID NO: 22), or (b) a fragment of (a) that retains the ability to bind NIK, or (c) a variant of (a) or (b) maintaining at least 90% identity with (a) or (b) and retaining the ability to bind NIK, or (d) a salt or functional derivative of (a), (b), or (c) that retains the ability to bind NIK, or (e) a circularly permutated derivative of (a), (b), or (c) that retains the ability to bind NIK wherein said polypeptide contains no more of the sequence of cyc (SEQ ID NO: 22) that the intracellular domain thereof (residues 284-369 of SEQ ID NO: 22).

The '073 patent teaches peptide-based substrate inhibitors of NIK, including PKI (protein kinase inhibitors) and staurosporine (column 4, lines 30-55; and column 5, Table II). Table II, for example (see column 5) recites selected peptidyl NIK kinase inhibitors, including IKK, TRAF2 and TRAF6. TRAF2, for example, is taught as capable of binding to NIK (column 1, lines 64-67 to column 2, lines 1-6) and comprises a functional derivative (see claim 104, part d) of a variant (see claim 104, part c) of a fragment (see claim 104, part b) of residues 284-369 of SEQ ID NO: 22 (e.g. double serine residues, SS).

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CMW

Marianne P. Allen

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PRIMARY EXAMINER

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